US Army Medical Research and Materiel

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Previns as Specific Inhibitors and Therapeutic Agents for Botulinum Toxin B and Tetanus Neurotoxins

Features and advantages:

- **Can prepare synthetically or using recombinant DNA expression systems**
- **Could administer alone or mixed with additional protease inhibitors or adjunct chemicals**
- **Could potentially use to detect BoNT/B and tetanus toxin through selective inhibition**
- **Could potentially use to detoxify food or wounds by sprinkling with a mixture or powder**
- **Could potentially use in a breathing mask to inactivate aerosol**

This invention relates to the discovery and preparation of a new class of peptide and peptide-like compounds, “Previns”, which are core structures that have an internal QF bond and the ability to inhibit Botulinum neurotoxin (BoNT) B protease activity. Previns may be used to construct compounds such as Buforinins (e.g., Buforin I) and other analogous peptides that also have a QF bond. Since the tetanus and the BoNT/B cleavage sites are the same, Previns may competitively inhibit tetanus protease activity.

BoNTs are among the most potent toxins to animals and humans, e.g., the lethal dose required to kill 50 % of mice exposed to BoNTs (LD_{50}) is about 1 ng/kg. BoNTs comprise a family of seven distinct serotypes, A – G. BoNTs are composed of two subunits, consisting of a 100 kdal nerve cell targeting heavy chain and a 50 kdal endoproteolytically active light chain. The BoNTs are zinc metalloproteases and contain a zinc protein binding motif. Zinc metalloprotease inhibitors exist but are not effective against BoNTs; they merely delay the protease activity *in vivo*. Inhibitors of the various serotypes, including BoNT/B, are therefore needed.

The Previn core structures or compounds containing them may be linked to the heavy chain end of the BoNT/B through a disulfide bond, or through a carrier protein such as human albumin to form a conjugate. The conjugate [illegible]hen target the susceptible cells in a manner similar to BoNT/B. Once inside the cell, the conjugate may inhibit BoNT/B or the linkage may be cleaved to free the compound containing the core structure or carrier-core [illegible]e to inhibit BoNT/B protease activity. Subjects [illegible]otentially be treated with Previns through [illegible]travenous injection or a patch prior to entering situations where contact with BoNT/B or tetanus toxins is likely.

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